IN THE UNITED STATES PATENT AND TRADEMARK OFFICE



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| Applicants: | David A. Cheresh et al. | ) |
| Application No. | 09/538,248 | ) |
| Filed: | March 29, 2000 | ) |
| | | ) Group Art Unit: 1652 |
| For: | METHODS USEFUL FOR TREATING VASCULAR LEAKAGE AND EDEMA USING SRC OR YES TYROSINE KINASE INHIBITORS | ) |
| Examiner: | Rebecca Prouty | ) Attorney Docket No. TSRI 651.3 |

**DECLARATION OF DAVID A. CHERESH, Ph.D.**

Commissioner for Patents
Washington, D. C. 20231

Sir:

DAVID A. CHERESH declares:

1. That I am one of the named inventors in the above-identified patent application;

2. That my *curriculum vitae* is attached hereto as Exhibit A;

3. That I am familiar with the subject matter described and claimed in the above-identified application;

4. That I have read the Office Action dated October 2, 2002 on the above-identified application and the prior art references relied upon by the Examiner;

5. That the presently claimed subject matter, namely subject matter defined by claims 1-4 and 16-20, inclusive, would not have been obvious to one of ordinary skill in the art of treating tissue damage due to vascular edema because (1) there is no reasonable expectation of success that the inhibition of Src kinase would lead to a successful inhibition of vascular edema or to reduced tissue damage due to such edema, (2) there are many pathways for activating Src kinase, and (3) different means of activating Src kinase lead to different downstream effects, as discussed in detail hereinbelow and shown in the noted scientific publications;

6. That Losordo et al., Circulation 98:2800-2804 (1998), Exhibit B hereto, reports at page 2803 that therapeutic angiogenesis in patients with limb and myocardial ischemia may be achieved by treatment with VEGF, and that such statements by Losordo et al. would have led one of ordinary skill away from suppression of any component of the VEGF signaling pathways, including Src family tyrosine kinase;.

7. That Hayashi et al., Journal of Cerebral Blood Flow and Metabolism 18:887-895 (1998), Exhibit E hereto, expressly teaches that treatment with VEGF significantly reduces ischemic brain damage such as infarct volume and edema formation;

8. That, as noted by He et al., J. Biological Chemistry 274(35):25130-25135 (1999) (applied reference) and by Dvorak et al., American Journal of Pathology 146(5):1029-1039 (1995), Exhibit H hereto, more than one VEGF signaling pathway is known;

9. That Bao et al., Acta Pharmacol. Sin. 20(4):313-318 (1999), Exhibit F hereto, presents the hypothesis that reducing VEGF production or inhibiting VEGF signaling should negatively impact ischemic tissues and reports that intraventricular administration of anti-VEGF antibody increased the infarct size in a mouse cerebral ischemia model, and that this publication also would have discouraged one of ordinary skill from considering inactivation of any component of a VEGF signaling pathway ;

10. That there are many growth factor pathways for activating Src family tyrosine kinases; see, for example, Thomas et al. (Exhibit C) and Erpel et al., Current Opinion in Cell Biology 7:176-182 (1995), Fig. 1 at page 177, Exhibit G hereto, but only VEGF is known to induce vascular permeability;

11. That Src family tyrosine kinase is activated, *inter alia*, by angiogenesis growth factors such as FGF and VEGF [Thomas et al., Ann. Rev. Cell Dev. Biol. 13:513-609 (1997), at 536, Table 3, and at 557 (Exhibit C) and Zhan et al., J. Biol. Chem. 269(32):20221-20224 (1994) (Exhibit D)], but that VEGF is the only known angiogenesis growth factor that promotes vascular permeability; thus, one of ordinary skill would have had no reason to selectively target Src family tyrosine kinase so as to interfere with VEGF induced vascular permeability;

12. That one of ordinary skill seeking to promote tissue repair or reduce tissue damage would have been more likely to enhance VEGF activity rather than diminish it;

13. That Src family tyrosine kinase activation is one of many VEGF dependent signaling activities, thus one of ordinary skill would have had no motivation to consider Src family tyrosine kinase for inactivation even if the objective was to block VEGF induced vascular permeability;

14. That, as noted by Munshi et al., J. Immunology 164(3):1169-1174 (2000) (cited reference) and Dvorak et al. (Exhibit H), VEGF is a multifunctional cytokine that binds to a tyrosine kinase receptor found primarily in vascular cells, whereas Src family tyrosine kinases are non-receptor kinases found in all cells, thus the blocking of VEGF is not equivalent to blocking of Src family tyrosine kinases;

15. That whereas VEGF knockout mice do not develop normal vasculature and die *in utero*, Src kinase knockout mice do develop normal vasculature and survive to adulthood;

16. That none of the cited references by van Bruggen et al., Aiello et al., and Jirousek et al. suggest that the activation of Src family kinases is responsible for increased vascular permeability;

17. That the aforementioned publication by He et al. (applied reference) at page 25132 states that the relationship between c-Src activation and the physiological actions of VEGF is not understood, and at page 25130 states that post receptor signaling pathways are not yet fully understood;

18. That the role and identity of growth factors that control the extent of tissue damage and its repair are poorly understood; see, for example, Issa, R., Lab Invest. 79:417-425 (1999), Exhibit I hereto;

19. That the cited Munshi et al. publication does not suggest inhibition of vascular permeability, nor does this publication suggest that PP1 is a VEGF antagonist or inhibitor; see, for example, page 1171;

20. That I am not aware of any scientific basis for the contention that "PP1 would be expected to have similar therapeutic effects as the VEGF inhibitors of van Bruggen et al."; and

21. That the cited references by Aiello et al. or Jirousek et al. do not describe VEGF inhibitors.

I, DAVID A. CHERESH, the undersigned declarant, declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the above-identified patent application or any patent issuing thereon.

La Jolla, California

Date: 3/5/03

David A. Cheresh

# CURRICULUM VITAE


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|---|---|
| Name: | David A. Cheresh, Ph.D. |
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| Office Telephone: | (858) 784-8281 |
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| E. Mail: | cheresh@scripps.edu |
| Personal: | Date of Birth: May 6, 1953<br>Place of Birth: Detroit, MI |


## Positions Held:

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| 1996-Present | Professor<br>Depts. of Immunology & Vascular Biology, TSRI |
| 1989-1996 | Associate Professor<br>Department of Immunology, The Scripps Research Institute |
| 1985-1989 | Assistant Professor<br>Department of Immunology, The Scripps Research Institute |
| 1984-1985 | Senior Research Associate<br>Research Institute of Scripps Clinic |
| 1982-1984 | Postdoctoral Fellow<br>Research Institute of Scripps Clinic |
| 1979-1982 | Graduate Assistant Instructor<br>Department of Microbiology, University of Miami, Florida |
| 1976-1978 | Instructor, Microbiology<br>Florida International University, Miami, Florida |

## Education:

1982 Ph.D. Degree, Microbiology/Immunology, "A Mechanism of Immune Hyporesponsiveness in the Metastatic Breast Cancer Patient" University of Miami, Florida

1978 Masters Degree, Microbiology, "Characterization of a Non-productive Infection of HSV-2 in an SV-40 Transformed Hamster Cell" University of Miami, Florida

1975 B.S. Degree, Biology, University of Michigan, Ann Arbor, Michigan

## Professional Societies:

American Association for Cancer Research
American Society for Microbiology
American Society for Cell Biology
Society for Complex Carbohydrates

EXHIBIT A

## Honors/Awards and Administration:

2002 Organizer, Keystone Symposium "Cell Biological Response to the Extracellular Matrix"
Keynote Speaker, Society for Biological Therapy "Understanding Angiogenesis with Molecular Mechanisms"

2001 Fellow of the American Heart Association (F.A.H.A.)
Organizer, Gordon Conference, "Angiogenesis"

2000 Chair, AACR Special Conferences in Cancer Research, "Angiogenesis & Cancer"
Organizer, Gordon Conference, "Vascular Cell Biology"

1999 Recipient, 75th Anniversary Spirit of Scripps Award
Co-Chair, Gordon Conference, "Angiogenesis and Microcirculation"

1998 Director of The Scripps/Merck Joint Program on Angiogenesis
National Cancer Institute MERIT AWARD CA50286 - 1998-2006
Brooks, et al. Cell 85:1-20,1996 chosen as most cited "Hot Paper" by The Scientist in the field of Cell Biology
Presidential Symposium Lecture, American Society of Hematology Miami, Florida
7th Annual Dennis Woznicki Lecturer in Cardiovascular Pathology, Baylor College of Medicine, Houston, Texas
First Recipient of the Robert Bear Lectureship, St. Michael's Hospital, University of Toronto, Toronto, Ontario, Canada
"Visiting Professor in Oncology," McGill University & The University of Montreal, Montreal, Quebec, Canada
Keynote address, Weinstein Cardiovascular Research Conference, Vanderbilt University, Nashville, TN
Organizer, Keystone Symposium, "Angiogenesis & Vascular Remodeling" Steamboat Springs, CO

1997 Myron Karon Memorial Lecturer, Children's Hospital at Los Angeles
XXIII Recipient of the Myron Karon Memorial Lectureship, University of Southern California, Los Angeles, California
15th Hans Lindner Memorial Lecture, Weizmann Institute of Science, Rehovot, Israel
Broadhurst Lecture, Schepens Institute, Harvard Medical School, Boston, MA
Deans Symposium Lecture, Medical College of Georgia, Augusta, GA
Member, Pathobiochemistry Study Section, NIH

1996 Robert Flynn Professorship Award, Lecture, Tufts University School of Medicine, Boston, MA, October 31, 1996
Organizer, Keystone Symposium: Integrins and Signaling Events in Cell Biology and Disease, Keystone, CO.
Donald and Darlene Shiley Lectureship, "Starving Tumors," La Jolla, CA

1992 Recipient of the American Cancer Society Faculty Research Award, 1992-1997.

1990 Cheresh et al. Cell 57:59,1989 chosen as most cited "Hot Paper" by The Scientist in the field of Cell Biology

1988 "Distinguished Visitor" Anti-Cancer Foundation, Australia

1985 Recipient of the J. Ernest Ayre Memorial Junior Faculty Award given by the National Cancer Cytology Center

## Editorial and Review Boards:

2000-2003 Keystone Symposia, Scientific Advisory Board
1999-Present Endothelium, Journal of Endothelial Cell Research, Editorial Board
1999-Present Expert Reviews in Molecular Medicine, Editorial Board
1998-Present Molecular Medicine, Advisory Editorial Board
1998-Present Circulation Research, Editorial Board Member
1997-Present Microvascular Research, Associate Editor
1997-Present Angiogenesis Research, Associate Editor
1997-Present Angiogenesis, Editorial Advisory Board
1997-Present Journal of Clinical Investigation, Board of Consulting Editors
1997-2001 NIH Pathobiochemistry Study Section
1995-1998 National American Heart Association Grant Reviewer
1992-Present Journal of Cell Science, Associate Editor
1992-Present Cell Adhesion and Communication, Associate Editor
1992 Volume Editor, "Receptors for the Extracellular Matrix" Biology of the Extracellular Matrix Academic Press.

## Invited Lecturer:

2002 University of California San Diego, Cardiovascular Science Conference, San Diego, CA
The Center for Biomedical Continuing Education, 4th International Symposium on Anti-Angiogenic Agents, Dallas, TX
Keystone Symposia on Biological Response to the Extracellular Matrix, Banff, Canada
Keystone Symposia on Protein Phosphorylation & Mechanisms of Cellular Regulation, Taos, NM
St. Jude Children's Hospital, Education Program, Memphis, TN
Cold Spring Harbor Laboratories, 67th Symposium on Quantitative Biology "The Cardiovascular System", Cold Spring Harbor, NY
University of Texas, Pharmacology Seminar Series, Dallas, TX
Gordon Research Conference, Signaling by Adhesion Receptors, New London, CT
Breast Cancer International Research Group, 3rd International Conference, Anaheim, CA
The Center for Biomedical Continuing Education, 1st Annual Symposium on Anti-Receptor Signaling in Human Neoplasia, Chicago, IL
Society for Biological Therapy, Angiogenesis Workshop, San Diego, CA
American Society for Matrix Biology Conference, Houston, TX
American Society for Cell Biology Symposium Lecture, 42nd Annual Mtg., San Francisco, CA
2001 Gordon Research Conference, Fibronectin, Integrins and Related Molecules, Ventura, CA
Keystone Symposium, Cell Migration and Invasion, Tahoe City, CA
Stanford University School of Medicine, Stanford, CA
SUNY Stony Brook, School of Medicine, Scholars in Cancer Research, Stony Brook, NY
University of Wisconsin, Frontiers in Pharmacology, Madison, WI
Keystone Symposia on Molecular & Cellular Biology, Keystone, CO
2000 Keystone Symposia on Molecular & Cellular Biology, Joint Regulation of Signaling Pathways by Integrins & Growth Factors, Breckenridge, CO
Gordon Research Conference, Signaling by Adhesion Receptors, Newport, RI
Chair, Gordon Research Conference, Vascular Cell Biology, Plymouth, NH
Keystone Symposia on The Dynamics of the Cytoskeleton/Intercellular Junctions, Keystone, CO.
Biomedical Sciences Seminar Series, UCSF, San Francisco, CA
Keystone Symposia on Experimental & Clinical Regulation of Angiogenesis, Salt Lake City, Utah
Experimental Biology 2000 (FASEB), Signal Transduction & Angiogenesis, San Diego, CA
John Wayne Cancer Institute Seminar, Santa Monica, CA

UCSD/Salk Institute Mahajani Symposium, La Jolla CA
Georgetown University Medical Center, Oncology Grand Rounds, Washington, D.C.
AACR Special Conference on Angiogenesis, Traverse City, MI
Angiogenesis Seminar, The Wistar Institute, Philadelphia, PA
American Heart Association, Council on Arteriosclerosis, Thrombosis and Vascular Biology, New Orleans, LA

1999 UIC Gynecologic Oncology Group Symposium, Nashville, TN
First International Symposium on Anti-Angiogenic Agents, Irving, TX
The Gynecological Oncology Research Group Lecture Series, Boston, MA
Beth Israel Deaconess Medical Center, Boston, MA
IBC's 5th Annual Conference on Angiogenesis, Boston, MA
Keynote Speaker, Robert Wood Johnson Medical School, 1st Annual Research Day, New Brunswick, NJ
Vascular Biology '99, Matrix Remodeling in Angiogenesis, Washington, DC
University of North Carolina Lineberger Comprehensive Cancer Center, Chapel Hill, NC
Gordon Research Conference, Molecular Cell Biology, Tilton, NH
ISHR, Cardiovascular Research in the new Millennium - XXI Century, XXI Annual Scientific Sessions, San Diego, CA
NCI, Third National AIDS Malignancy Conference, Bethesda, MD
Gordon Research Conference, Cell Contact and Adhesion , Proctor Academy, NH
Gordon Research Conference, Angiogenesis & Microcirculation, Salve Regina University, Newport, RI
Georgetown University Medical Center, 1999 Oncology Grand Rounds,Washington, DC
Ludwig Institute for Cancer Research, Salk Institute, Cancer on the Eve of the Millennium: Diagnostics, Therapy & Prevention, San Diego, CA
AACR Special Conference, Molecular Aspects of Metastasis, Snowmass, CO
Horizons in Vascular Biology & Therapeutics, Miami, FL

1998 Keystone Symposia Conference, Wound Repair, Copper Mountain, CO
AACR Special Conference, Angiogenesis and Cancer, Orlando, FL
Keystone Symposia Conference, Motility and Metastasis, Copper Mountain, CO
Keystone Symposia Conference, Endothelium, Lake Tahoe, NV
Keystone Symposia Conference, Molecular Biology of the Cardiovascular System, Steamboat Springs, CO
Keystone Symposia Conference, Angiogenesis and Vascular Remodeling, Steamboat Springs, CO
2nd International Symposium, Science and Medicine, Vascular Protection: From Basic Science to the Clinic, Los Angeles, CA
BACR/IACR Joint Annual Scientific Meeting, Dublin, Ireland
Brazilian Symposium on Extracellular Matrix, Rio de Janeiro, Brazil
VII International Congress of the Metastasis Research Society, San Diego, CA
1st Annual Robert Bear Lectureship, Toronto, Ontario, Canada
Schering Foundation Workshop, Therapeutic Angiogenesis: From Basic Science to the Clinic, San Francisco, CA
1998 Annual Meeting of the American Society of Hematology, Miami Beach, FL
Science & Medicine Second International Symposium, Vascular Protection: From Basic Science to the Clinic, Los Angeles, CA

## Bibliography:


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2. Cheresh, D.A., Distasio, J.A., Vogel, C.L. and Lopez, D.M. Mitogen-induced blastogenesis and receptor mobility inhibition by breast cancer serum with elevated orosomucoid (a1-acid glycoprotein) levels. *J. Natl. Cancer Institute* 68:779-783. 1982.

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